27. (Amended) An antibody-based fusion protein comprising a variable domain and a portion of an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein, wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein.

REMARKS

In the Office Action, claims 14-24 and 26 were withdrawn from consideration. Claims 1-4, 6-13 and 27 were considered. Claims 2 and 27 were rejected under 35 U.S.C. §112, first paragraph. Claims 1, 3, 6-9 and 13 were rejected under 35 U.S.C. § 102(b). Claims 1, 3, 4, 6-9, 10-13 and 27 were rejected under 35 U.S.C. §103(a). Claims 1 and 27 have been amended. Upon entry of this amendment, claims 1-4, 6-13 and 27 will be pending for further examination.

Reconsideration and withdrawal of all of the outstanding rejections is respectfully requested in view of the present claim amendments and remarks.

Claim Amendments

The claims have been amended to further clarify the claimed subject matter. Basis for the claim amendments can be found in the specification, including the claims as originally filed.

Specifically, basis for the recitation of claim 1 of an antibody-based fusion protein comprising at least a portion of a CH2 domain, wherein said portion comprises a domain required for immunoglobulin protection receptor (FcRp) binding affinity can be found, *inter alia*, in original claim 5, in the specification at least on page 8, lines 13-24 and in Example 2.

Furthermore, claim 27 is amended to recite an antibody-based fusion protein comprising a variable domain and a portion of an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein, wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein. Basis for amended claim 27 can be found in the specification, *inter alia*, at page 3, lines 8-11 and in Example 1, section 1.1.

Applicants submit that these amendments introduce no new matter.

Remarks Regarding Rejections:

The following comments address the claim rejections in the order that they were raised in the Office Action.

Claim Rejections Under 35 U.S.C. §112, second paragraph

The Office Action rejected claims 2 and 27 under 35 U.S.C. §112, first paragraph. Specifically, the Office Action alleges that the "specification...does not provide support for the invention as now claimed: an antibody-based fusion protein which has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein" (see the Office Action at page 2). Applicants respectfully submit that support for the above mentioned limitation is provided in the specification, *inter alia*, on page 7, lines 5-8; page 12, lines 15-17; page 13, lines 15-19; and page 14, lines 7-21.

Therefore, Applicants respectfully request that the rejection of claims 2 and 27 under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. §102

The Office Action rejected claims 1, 3, 6-9 and 13 under 35 U.S.C. §102(b) as anticipated by Hoogenboom et al., Molecular Immunology, Vol. 28, No. 9, pp. 1027-1037 (1991) (hereinafter Hoogenboom et al.). As indicated in the Office Action, Hoogenboom et al. reports an "antibody-TNF fusion construct, [wherein] the human TNF gene is linked to the CH2 domain of the human gamma-1 chain." The Office Action further indicates that "in this construct, Leu-235 was deleted, thus decreasing binding of the antibody-TNF fusion protein to Fc receptors" (see the Office Action at page 4).

A proper rejection under 35 U.S.C. §102 requires that a cited reference disclose all the limitations of the rejected claims. Applicants respectfully submit that Hoogenboom et al. fails to disclose all the limitations of Claim 1. Specifically, Hoogenboom et al. fails to disclose a fusion protein comprising a portion of a CH2 domain comprising a mutation or deletion that reduces binding affinity for an Fc receptor, but retains in the CH2 portion a domain having binding affinity for FcRp. Applicants respectfully submit that the fusion protein disclosed in

Hoogenboom et al. retains only the first 3 amino acids of an IgG1 CH2 domain and, thus, does not contain a portion of a CH2 domain required for FcRp binding affinity (see, *inter alia*, at least lines 13-24 on page 8 of the specification). Accordingly, Hoogenboom et al. does not disclose every element recited in claim 1 and, therefore, does not form the proper basis for continued rejection under 35 U.S.C. §102(b). Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 3, 6-9 and 13 depend from claim 1. As such, Applicants respectfully request that rejection of claims 3, 6-9 and 13 under 35 U.S.C. §102(b) also be withdrawn given the arguments set forth above.

Claim Rejections Under 35 U.S.C. §103

a) Rejections over Hoogenboom et al. and U.S. Patent No. 6,100,387

The Office Action rejected Claims 1, 3, 6-9, 13 and 27 under 35 U.S.C. §103(a) as unpatentable over Hoogenboom et al. in view of U.S. Patent No. 6,100,387 (hereinafter the '387 patent).

1) Claims 1, 3, 6-9 and 13

A proper rejection under 35 U.S.C. §103(a) requires that the cited references, when combined, disclose all the limitations of the rejected claims. As discussed above, Applicants submit that Hoogenboom et al. fails to disclose all the limitations of claims 1, 3, 6-9 and 13. Applicants further submit that the limitations absent in Hoogenboom et al. are not disclosed the '387 patent. The Office Action pointed to the disclosure in the '387 patent of a "chemokine-encoding fragment, a fragment containing a linker and part of the Fc portion of the IgG4 gene, a fragment containing the rest of the Fc portion of the IgG4 gene, and a vector fragment" (see the Office Action at pages 4-5). In contrast, claim 1 recites, "an antibody-based fusion protein comprising at least a portion of a CH2 domain,...wherein said CH2 domain is an IgG1 or an IgG3 CH2 domain...." Applicants respectfully submit that the combined references fail to teach an antibody based fusion protein comprising at least a portion of a CH2 domain, wherein said

portion comprises a domain required for immunoglobulin protection receptor (FcRp) binding affinity, linked to a non-Ig protein, wherein said CH2 domain is an IgG1 or an IgG3 CH2 domain.

Accordingly, the combined disclosures of Hoogenboom et al. and the '387 patent do not disclose every element recited in claim 1 and, therefore, do not form the proper basis for continued rejection under 35 U.S.C. §103(a). Claims 3, 6-9 and 13 depend from claim 1. As such, Applicants respectfully request that rejection of claims 1, 3, 6-9 and 13 under 35 U.S.C. §102(b) be withdrawn given the arguments set forth above.

2) Claim 27

The Office Action further rejected new claim 27 under 35 U.S.C. §103(a) as being unpatentable over Hoogenboom et al. in view of the '387 patent. Hoogenboom et al. does not disclose an antibody-based fusion protein that comprises the CH2 domain of an IgG4 constant region, as characterized by the Office Action (see the Office Action at page 4). Applicants submit that the '387 patent reports fusion proteins of a chemokine and an Fc portion of IgG4, wherein the chemokine portion is at the N-terminus of the fusion protein and the IgG4 Fc portion is at the C-terminus of the fusion protein (see column 20, lines 14-25). In contrast, claim 27 recites an antibody-based fusion protein comprising a variable domain and a portion of an IgG4 CH2 domain linked to a non-Ig protein, wherein the variable and CH2 domains are at the N-terminus of the fusion protein and the non-Ig protein is at the C-terminus of the fusion protein. Therefore, Applicants respectfully submit that the combined disclosures of Hoogenboom et al. and the '387 patent do not teach the recited limitations of claim 27.

Furthermore, Applicants submit that the cited references fail to provide any motivation or suggestion to include an immunoglobulin variable region in the IgG4 portion of the chemokine-Fc fusion protein. The Office Action alleges that "the motivation is provided in [the '387 patent] (column 24, Table 2 and 3), which shows the success of these antibody-based fusion polypeptides to bind to receptors expressed by several human cell lines" (see the Office Action page 5). Applicants respectfully submit that Tables 2 and 3 show results relating to binding of the SDF-1α-Fc fusion protein to SDF-1α receptors. As such, the Tables 2 and 3 demonstrate

receptor binding via the non-Ig protein, and not the Ig portion of the fusion protein, thus teaching away from adding a variable domain to the SDF-1α-Fc fusion protein.

Accordingly, the cited references not only fail to teach all the elements of claim 27 when combined, but also fail to provide any motivation or suggestion for their combination. Therefore, Applicants respectfully request that this rejection be reconsidered and withdrawn.

b) Rejections over Hoogenboom et al. and WO 97/30089

The Office Action also rejected claims 1, 4, 7-8 and 10-13 under 35 U.S.C. §103(a) as being unpatentable over Hoogenboom et al. in view of WO 97/30089. The Office Action points to a fusion protein that has "the N-terminus of human IL-2 fused to the C-terminus of IgG3, including the CH2 domain" and "binds the FcγRI with slightly lower affinity than that of IgG3 alone" (see the Office Action at page 6).

Applicants respectfully submit that the cited references fail to provide any motivation or suggestion to make alterations in an antibody-based fusion protein that retains in the IgG3 CH2 portion a domain having binding affinity for FcRp, but comprises a mutation or a deletion that reduces binding affinity for an Fc receptor. On the contrary, WO 97/30089 teaches that Fc receptor binding is an important and desired effector function exhibited by the disclosed fusion protein. Specifically, WO 97/30089 teaches that the Fc region of the IgG3, and its N-glycosylation site, are involved in Fc receptor binding. The reference further teaches that that the use of this glycosylation site in the fusion protein is "important to the effector functions of the molecule" (see page 16, fifth paragraph). In Figures 1A and 1B, the reference demonstrates that the Fc portion of the fusion protein is glycosylated and concludes therefrom that the fusion protein is expressed and post-translationally modified "as desired" (see page 16, fifth paragraph).

Additionally, as discussed above, Hoogenboom et al. fails to teach or suggest a fusion protein comprising a portion of a CH2 domain comprising a mutation or deletion that reduces binding affinity for an Fc receptor, but retaining in the CH2 portion a domain having binding affinity for FcRp. Therefore, Applicants respectfully submit that the cited references, taken alone or in combination, fail to teach or suggest the fusion protein of claim 1. Accordingly, Applicants respectfully request that this rejection of claim 1 be reconsidered and withdrawn.

Claims 4, 7-8 and 10-13 depend from claim 1. As such, Applicants respectfully request that rejection of claims 4, 7-8 and 10-13 under 35 U.S.C. §103(a) also be withdrawn given the arguments set forth above.

CONCLUSION

Applicants submit that on the basis of the foregoing remarks and claim amendments, claims 1-4, 6-13 and 27 are in condition for immediate allowance. Accordingly, Applicants respectfully requests entry as such. Should further issues of patentability be determined to exist, the Examiner is respectfully requested to contact the undersigned by telephone to expedite prosecution of this application.

Respectfully submitted,

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MARKED-UP CLAIMS SHOWING AMENDMENTS FOR U.S.S.N. 09/256,156

1. (Twice amended) An antibody-based fusion protein comprising at least a portion of a CH2 domain, wherein said portion comprises a domain required for immunoglobulin protection receptor (FcRp) binding affinity, linked to a non-Ig protein, wherein said CH2 domain is an IgG1 or an IgG3 CH2 domain comprising a mutation or a deletion that reduces binding affinity for an Fc receptor, and said antibody-based fusion protein has a longer circulating half-life *in vivo* than [~~an~~] said antibody-based fusion protein without said mutation or deletion.

27. (Amended) An antibody-based fusion protein comprising a variable domain and a portion of [a] an IgG4 CH2 domain, the C-terminus of which is linked to the N-terminus of a non-Ig protein, [~~wherein said CH2 domain is an IgG4 CH2 domain, and~~] wherein said antibody-based fusion protein has a longer circulating half-life *in vivo* than an antibody-based fusion protein comprising a portion of an IgG1 CH2 domain linked to said non-Ig protein.